

Comment on “A pilot trial of G3139, a *bcl-2* antisense oligonucleotide, and paclitaxel in patients with chemorefractory small-cell lung cancer”, by C. M. Rudin et al. (Ann Oncol 2002; 13: 539–545)

In their pilot study, Rudin et al. describe the safety, feasibility and toxicity profile of the combination of paclitaxel and G3139 (Genasense™), a *bcl-2* antisense oligonucleotide, in patients with chemoresistant small-cell lung cancer (SCLC). Tolerance of G3139 in these patients was good and further studies are ongoing.

Although ‘proof of principle’ was not the aim of the study, and because repeated tumor biopsy for the measurement of target protein expression in tumor cells was not possible, *bcl-2* protein expression was measured in peripheral-blood mononuclear cells (PBMCs) before and after the administration of G3139. A decrease in *bcl-2* protein in PBMCs may prove sustained biological activity upon G3139 i.v. infusion, however, it is not an accurate substitute for *bcl-2* expression in tumor cells, and therefore, no conclusions should be drawn from these results. We believe that, when studying antisense activity, analysis of the tumor cells must remain the gold-standard for target validation as long as no surrogate markers are available. It is especially necessary to evaluate potential surrogate markers, such as circulating tumor-specific protein, DNA and mRNA, for clinical studies of patients with tumors that are not readily accessible.

Another concern arises from the fact that untreated, as well as chemoresistant, SCLC cells express not only *bcl-2* but also *bcl-xL*, another potent anti-apoptotic protein, at remarkably high

levels [1]. Furthermore, tumor cells are able to switch expression from *bcl-2* to *bcl-xL* [2], resulting in sustained tumor cell survival. In order to adequately address this complication, we have developed a single ‘bispecific’ antisense oligonucleotide that simultaneously targets the *bcl-2* and *bcl-xL* mRNA. This compound has demonstrated inhibition of target protein expression, as well as potent antitumor efficacy, in preclinical models of various human tumors *in vitro* and *in vivo* [3].

The publication by Rudin et al. is an important step towards the broad therapeutic use of antisense oligonucleotides against malignant human tumors; we anticipate new challenges will arise when more of these promising compounds are carried from the bench to the clinic.

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